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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Application Number: 10/777,415
Filing Date: February 11, 2004
Appellant(s): SUBRAMANIAN ET AL.

Judy M.Mohr
Registration No. 38,563
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 09/25/08 appealing from the Office action mailed 04/25/08.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments after Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,252,338	JAO *et al.*	6-2003
4,717,566	ECKENHOFF *et al.*	2-1998
4,111,202	THEEUWES *et al.*	3-2001
WO 99/62496 ('496)	AYER *et. al.*	12-1999

Physiciens Desk Référence

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ayer et al. WO99/62496 ('496) in view of Jao et al. (US Patent No. 5,252,338) and further in view of Eckenhoff et al. (US Patent No. 4717566) and Theeuwes (US Patent No. 4,111,202).

2. Claims 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ayer et al. WO 99/62496 ('496) in view of Jao et al. (US patent no. 5,252,338) and further in view Of Eckenhoff et al. (US patent No. 4,717,566), Theeuwes (US Patent no. 4,111,202) and Physicians Desk Reference of record.

1. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ayer et al. (WO 99/62496 ('496)) in view of Jao et al. (US Patent No. 5,252,338) and further in view of Eckenhoff et al. (US Patent No. 4,717,566) and Theeuwes (US Patent No. 4,111,202).

Ayer et al. discloses methods and devices for maintaining a desired therapeutic drug effect over a prolonged therapy period. In particular, oral dosage forms that release drug within the gastrointestinal tract at an ascending release rate over an extended time period (abstract). Ayer et al. discloses bilayer and trilayer oral osmotic dosage forms. The bilayer has first component layer comprising a selected drug and excipients for forming a deliverable drug composition when hydrated and a second push layer, comprising a fluid expansion osmopolymer and excipients, contained within the compartment formed by a semi permeable membrane and having an exit means to release the drug. The two layers are compressed together to provide a longitudinally compressed tablet core having a shape of a "capsule shaped configuration. (See page 7, lines 5-17). The trilayer oral osmotic dosage forms include a novel trilayer tablet core surrounded by a semi permeable membrane and having suitable exit means for releasing the drug formulation through the semi permeable membrane. The tablet has a first drug containing layer, a second drug containing layer and a third push layer. During operation, the drug is successively released from the first drug containing layer and then from the second drug containing layer. The drug concentration gradient facilitates the achievement of an ascending drug release rate for an extended time period.

Consequently, the excipients in the drug-containing layer may be flexibly varied and adjusted for manufacturing convenience and the dosage forms thus exhibit drug release having the desired sustained and ascending rate over an extended time period. (See page 8, lines 1-10). Various drugs that are used are depicted on page 8, lines 25-30. Example 5 depicts trilayer oral osmotic dosage forms having a drug concentration variance wherein the viscosity of first component was lower than the second which in turn was lower than the third. The example shows an ascending release rate for an extended time period. Sequential compression of various component layers is shown on page 35, lines 15-20).

The reference does not teach delay layer as the first component layer, located adjacent to the exit orifice.

However, Jao et al. teach a dosage form comprising means for delaying delivery of drug from the dosage form following the administration of the drug (see drawings of figure 3-5). On column 4, Jao et al. show how the polymeric delay layer along with the drug in it helps in delaying the delivery of the drug. The polymeric means possesses a slow rate of hydration dependent on the molecular weight and viscosity. The dosage form can take wide variety of shapes such as oral and buccal etc. (see column 5, lines 34-35).

Jao et al. do not teach the convex geometry as claimed in an instant application, however, Eckenhoff et al. teach a dosage form for delivering a beneficial agent with a convex geometry. The dosage form comprises a wall that surrounds and defines an internal space, a composition comprising a beneficial agent, means for aiding beneficial

agent for delivering the composition. (See abstract and drawing on the abstract page and fig 30.).

Theeuwes teaches an osmotic system for the delivery of active agent over time. The system comprises a wall surrounding an agent compartment and an osmagent compartment separated by a film and has a passageway through the wall for delivering the agent from its compartment. (See abstract and the picture depicting convex configuration formed at the time of release.).

It would have been obvious to the one of ordinary skill in the art at the time the invention was made to incorporate a delay layer in place of first drug component in the dosage form of ('496) based on the teachings of Jao et al. and have an interface boundary between the delay layer and the drug layer having a convex configuration as taught by Eckenhoff and Theeuwes because the delay layer helps in delaying the delivery of the active agents from the dosage forms following the administration of the dosage form to a patient in need of drug therapy and the dosage form with the convex configuration as taught by Eckenhoff and Theeuwes successfully aid in delivering a beneficial agent. One skilled in the art would have been motivated to manipulate the viscosities of drug and the delay layer by the teachings of Jao et al. as Jao et al. teaches how the manipulations of viscosities can affect the release rates of the drug.

Motivated by the teachings of various dosage forms with specific geometrical configurations, as discussed in the aforementioned references, a skilled artisan would have prepared a dosage form comprising (a) a membrane defining a compartment, the membrane having an exit orifice formed or formable therein and at least a portion of the

membrane being semi permeable; (b) an expandable layer located within the compartment remote from the exit orifice and in fluid communication with the semi permeable portion of the membrane;(c) a delay layer located adjacent the exit orifice; (d) a drug layer located within the compartment between the delay layer and the expandable layer; and (e) an interface boundary between the delay layer and the drug layer, the interface boundary being convex in shape relative to the exit orifice with a reasonable expectation of success.

2. Claims 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable Over Ayer et al. (WO 99/62496 ('496)) in view of Jao et al. (US patent no. 5,252,338) and further in view of Eckenhoff et al. (US patent No. 4,717,566), Theeuwes (US Patent no. 4,111,202) and Physicians Desk Reference of record.

The references cited above do not specifically teach cyclobenzaprine. Physicians Desk Reference teaches that cyclobenzaprine HCl relieves skeletal muscle spasm. It would have been obvious to the one of ordinary skil in the art at the time the invention was made to make dosage form comprising cyclobenzaprine because of its therapeutic use. A skilled artisan would thus have been motivated to formulate a dosage form as claimed with a reasonable expectation of success.

(10) Response to Argument 1:

Appellants argue "that an informed consideration of the factors stated in *Graham v. John Deere* (383 U.S. 1, 148 USPQ 459 (1966)) leads to the conclusion that the claimed dosage form is not obvious in view of the cited references.

Appellants state that: With respect to the first factor, scope and content of the asserted art, Ayer *et al.* and Jao *et al.* describe osmotic dosage forms that include an osmotic "push layer" adjacent a drug layer the dosage form of Jao *et al.* includes, in the embodiment shown in Fig. 3, a delay layer (21) that surrounds the drug layer (16) and the osmotic push layer (18). Eckenhoff *et al.* describe a dosage form with a push layer (element 18 in Figs. 1-8), a drug layer (element 16 in Figs. 1-8), and a dense member (element 20 in Figs. 1-8) that serves to keep the dosage form in the rumen of an animal (Col. 5, lines 16-18). Theeuwes describes a dosage form having two compartments 13, 14 separated by a film or membrane 18 (col. 5, lines 27-35). Film 18 in Theeuwes when under pressure by an osmagent in compartment 14 is displaced, and as seen in Figs. IC-1F will be convex in shape.

With respect to the second factor, differences between claimed subject matter and the asserted art, Appellants note that none of the cited art shows a dosage form wherein the interface boundary between the delay layer and the drug layer is convex in shape relative to the exit orifice in the dosage form. To provide this element, the rejection relies on the drawings in Eckenhoff *et al.* and in Theeuwes, which show, a convex interface between a dense member (20) and a push layer (18) (Eckenhoff *et al.),* between a push layer (18) and a drug layer (16) (Eckenhoff *et al.),* or between a flexible film and a push layer (Theeuwes) between the delay layer and the drug layer is

convex in shape relative to he exit orifice in the dosage form. To provide this element, the rejection relies on the drawings in Eckenhoff *et al.* and in Theeuwes, which show, a convex interface between a dense member (20) and a push layer (18) (Eckenhoff *et al.),* between a push layer (18) and a drug layer (16) (Eckenhoff *et al.),* or between a flexible film and a push layer (Theeuwes). Appellant further argues that modifications of the teachings of cited references are a questionable parameter without giving hindsight benefit.

Appellant's arguments are not persuasive.

In response to appellants arguments that claimed dosage form is not obvious over the cited references, the Examiner respectfully recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The claims are given broadest reasonable interpretation during prosecution. The instant independent claim requires:

A dosage form comprising

(a) a membrane defining a compartment, the membrane having an exit orifice formed or formable therein and at least a portion of the membrane being semi permeable;

(b) an expandable layer located within the compartment remote from the exit orifice and in fluid communication with the semipermeable portion of the membrane;

(c) a delay layer located adjacent the exit orifice;

(d) a drug layer located within the compartment between the delay layer and the expandable layer; and

(e) an interface boundary between the delay layer and the drug layer, the interface boundary being convex in shape relative to the exit orifice.

Dependent claims require compression sequence and state the viscosity requirements and specific drug requirements in the dosage form.

Ayer et al. discloses an osmotic device for prolonged therapy (see abstract). The reference teaches a dosage form with first component layer comprising a selected drug and excipients for forming a deliverable drug composition when hydrated and a second push layer, comprising a fluid expansion osmopolymer and excipients, contained within the compartment formed by a semi permeable membrane and having an exit means to release the drug. The two layers are compressed together to provide a longitudinally compressed tablet core having a shape of a "capsule shaped configuration. (See page 7, lines 5-17).

What are lacking in Ayer et al. are the delay layer and the interface boundary. Jao et al. has been to teach a dosage form comprising means for delaying delivery of drug from the dosage form following the administration of the drug (see drawings of figure 3-5). On column 4, Jao et al. show how the polymeric delay layer along with the drug in it helps in delaying the delivery of the drug. The polymeric means possesses a slow rate of hydration dependent on the molecular weight and viscosity. The dosage form can take wide variety of shapes such as oral and buccal etc. (see column 5, lines 34-35).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to incorporate the delay layer in the teachings of Ayer et al. because the purpose of Ayer et al. is to provide a desired therapeutic drug effect over a prolonged period. One would have been motivated to provide delayed layer in the teachings of Ayer et al. because Jao et al. teach benefit of delay layer in delaying the drug delivery.

The combined teachings of Ayer et al. and Jao et al. do not teach the interface boundary. However, in an analogous art, Eckenhoff et al. teach a dosage form for delivering a beneficial agent with a convex geometry. The dosage form comprises a wall that surrounds and defines an internal space, a composition comprising a beneficial agent, means for aiding beneficial agent for delivering the composition. (See abstract and drawing on the abstract page and fig 30) and Theeuwes teaches an osmotic system for the delivery of active agent over time. The system comprises a wall surrounding an agent compartment and an osmagent compartment separated by a film and has a passageway through the wall for delivering the agent from its compartment. (See abstract and the picture depicting convex configuration formed at the time of release.).

The following shows convex geometry in Eckenhoff et al.

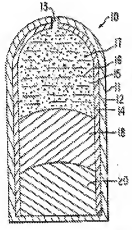
13
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FIG. 2

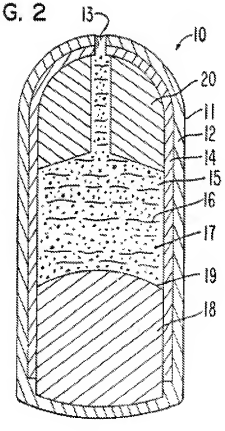
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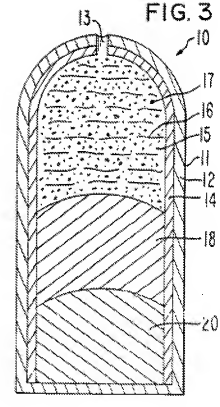
FIG. 3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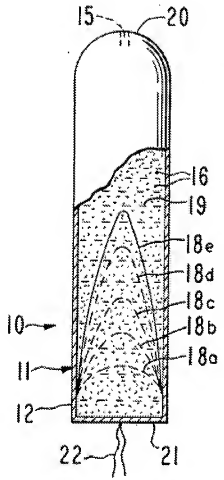
The following shows convex geometry in Theeuwes reference:



Motivated by the teachings of Eckenhoff et al. and Theeuwes depicting and describing convex geometry of osmotic dosage for aiding beneficial agent for delivering the composition, it would have been obvious to one of ordinary skill in the art at the time of instant invention to incorporate the convex geometry and come to the claimed invention with a reasonable expectation of success. Appellant has not shown any

unexpected results associated with the claimed geometry where the teachings of the prior art clearly show the claimed features in an analogous art.

Regarding applicant's arguments that none of the references show the claimed geometry, it is the position of the examiner that only Eckenhoff and Theeuwes references were cited for the convex geometry, not all the references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Appellant argues that "In Eckenhoff *et al.,* convex-shaped layers 18, 20 are illustrated in some of the drawings *(i.e.,* Figs. 1-5, 7, and 8). However, a reading of Eckenhoff *et al.* reveals that neither of the convex shaped layers is a delay layer. Instead, convex layer 18 corresponds to an expandable member (or "push layer") of the

dosage form (col. 9, line 48 - col. 10, line 18), and convex layer 20 corresponds to a dense member that has a high specific gravity to *prevent* the passage of the dosage form from the rumen *(e.g.,* col. 12, lines 36-65). Neither the expandable member 18 nor the dense member 20 is equivalent to a *delay layer,* nor is the interface between the expandable member 18 and the dense member 20 equivalent to an interface boundary between a delay layer and a drug layer. Nor would the expandable member 18 and the dense member 20 serve the equivalent function of a delay layer in a dosage form.
With respect to Theeuwes, the film or membrane 18 separates a first compartment 13 contains a beneficial agent/drug 16 (col. 5, lines 4-6) from a second compartment 14 that contains an osmagent 17 *(i.e.,* "push layer;" col. 5, lines 19-26). It is, therefore, apparent that film 18 is not equivalent to an interface boundary between a delay layer and a drug layer, nor would it serve the equivalent function in a dosage form.
It appears to be the Examiner's position that the fortuitous illustrations of a *convex shape* in Eckenhoff *et al.* and Theeuwes renders it obvious for a skilled artisan to apply the convex shape to an interface between layers in a dosage form, and in particular to an interface between a drug layer and a delay layer. Neither Eckenhoff *et al.* nor Theeuwes describe interfaces between layers, let alone a convex interface. Nor is there any mention of any advantage to a convex interface between layers in a dosage form.

Appellant's arguments are not persuasive, as discussed supra, the analogous art by Eckenhoff et al. teach a dosage form for delivering a beneficial agent with a convex geometry. The dosage form comprises a wall that surrounds and defines an internal

space, a composition comprising a beneficial agent, means for aiding beneficial agent for delivering the composition. (See abstract and drawing on the abstract page and fig 30) and Theeuwes teaches an osmotic system for the delivery of active agent over time. The system comprises a wall surrounding an agent compartment and an osmagent compartment separated by a film and has a passageway through the wall for delivering the agent from its compartment. (See abstract and the picture depicting convex configuration formed at the time of release.).

Motivated by the teachings of Eckenhoff et al. and Theeuwes depicting and describing convex geometry of osmotic dosage for aiding beneficial agent for delivering the composition, it would have been obvious to one of ordinary skill in the art at the time of instant invention to incorporate the convex geometry and come to the claimed invention with a reasonable expectation of success. Appellants have not shown any unexpected results associated with the claimed geometry where the teachings of the prior art clearly show the claimed features in an analogous art.

Appellant further asks the Board to carefully and mindfully question whether a skilled artisan would actually look at Eckenhoff *et al.* and Theeuwes and imagine taking a feature illustrated in the drawings, but not mentioned or discussed in the text, and applying that feature to a dosage form arrived at by combining Ayer *et al.* with Jao *et al,* and more specifically applying that illustrated feature to the drug/delay layers and not, for example to other layers, such as the push/drug layer. Absent the instant specification, Appellants simply fail to see the link to make these choices.

Appellants arguments are not persuasive because Eckenhoff describes under "brief description of the Drawing" all the figures and Theeuwes provides description for all the figures under detailed description of drawings. Additionally, the rationale behind this argument is not entirely clear to the examiner because whether in picture or in description, the references teach the required features of recited instant claims. Even assuming that the reference does not suggest convex shape in text, the examiner points out that brief description of Fig. 13 on page 34, paragraph [000125] of instant specification indicates only an optimal performance.

([000125] Figure 13 illustrates the resulting layer interfaces from the present invention. The traditional compression sequence is inverted, reversed, such that the natural shape of the layer interfaces from compression is inverted to be convex relative to the exit orifice for optimal performance.)
It is the position of the examiner that optimum performance is not an unexpected result.

(11) Response to Argument 2:

Appellant argues that additional reference reciting specific drug does not cure the deficiency of the rejections of claims 1-4, as such the rejections should be withdrawn.

Appellant's arguments are not persuasive, as discussed supra, the rationale to combine teachings of Ayer et al., Jao et al., Eckenhoff and theeuwes have been cited above. Appellants have not argued merits of Physician's desk reference separately,

thus, given the explicit teachings of the prior art identified above, it is the position of the Examiner, that the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

(12) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Snigdha Maewall

/Snigdha Maewall/

Examiner, Art Unit 1612

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